

Original article

Quality Assessment of RCTs in Cochrane Breast Cancer Review group

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Abstract:

Introduction: High-quality systematic reviews provide dependable evidence for medical interventions. Bias in Randomized controlled trials may overvalue or undervalue the efficacy of an intervention. There are few systematic reviews which contain all eligible articles on the special issue and thus present the highest quality evidence. Since breast cancer is the most common neoplasm in females, we aim to determine the variations in the risk of bias for randomized controlled trials included in The Cochrane breast cancer review group.

Methods: This study was done as a review of RCTs included in Cochrane breast cancer systematic reviews until October 2015. Overall, 47 reviews which included 587 RCTs, were studied to determine the risk of selection, performance, detection, attrition and reporting bias by The Cochrane Collaboration's "Risk of Bias" tool. Then, data was analyzed by Microsoft Excel 2013 for frequency analyses. Finally, it was assessed if authors have gotten a specific conclusion or not.

Findings: The search identified 50 reviews that 3 of them were excluded because of no RCTs inclusion. Finally, 587 RCTs were included for analysis. This study showed that the most and the least reported bias were allocation concealment and detection bias, respectively, which was reported in 93.6% and 48.2% of RCTs. Among 47 included systematic reviews, 33 of them could get a conclusion due to an adequate amount of evidence for their included RCTs and other 14 reviews needed more studies to get a conclusion.

Conclusion: According to the results, there was not any study with the only low risk of bias in all categories of bias, so it's concluded that adequate high evidence-based studies such as RCTs are missing in the field of breast cancer.

Keywords: Cochrane breast cancer review group, Randomized controlled trial, risk of bias

Introduction:

Evidence-based medicine offers the most trustworthy evidence for healthcare providers to optimize policymaking in diagnosis and treatment of the patients (1, 2). There was an increasing attention in evidence-based approaches for playing role in health programs and research, since the 1990s. Systematic reviews are main components for Evidence-based Medicine and among them; High-quality systematic reviews provide dependable evidence for medical interventions (3-5).

Cochrane collaboration has been pioneering systematic review organization since 1993. According to Cochrane strategies, only high-quality systematic reviews are elected to be published in Cochrane Library. High-quality reviews are reliable because they declare exact inclusion criteria of all studies and include the studies with low risk of bias. There are few systematic reviews which include all qualified articles on the special topic and present the maximum quality evidence. Several biases such as selection, performance, detection, attrition and reporting biases, affect the eligibility of systematic reviews. Selection bias presents the deficiency in random sequence generation and allocation concealment, whereas performance and detection biases present the lack of blinding of participants and evaluators, respectively. Attrition bias means incomplete outcome data that occurs when evaluations are not prepared for each main outcome. Reporting bias refers to lack in reporting the results of the study. Other causes of bias not mentioned above, are categorized as other biases (6).

Quality assessment of all included randomized controlled trials is reported by high risk, unclear risk, and low risk of bias for each bias category (7-10). Due to the high incidence of breast cancer in females as a worldwide concern, in recent years, the importance of reviews in diagnosis and

treatment of the disease, and also the effect of quality of RCTs in the reliability of reviews, we aim to evaluate the quality of included articles in the Cochrane systematic reviews of Breast Cancer by their bias state to represent that whether health care providers can rely on conclusions of these reviews or the results are not reliable because of the high risk of bias.

Methods:

This study was designed as a review for evaluating the quality of systematic reviews. We searched the Cochrane library based on Cochrane medical terms search for all the reviews relating breast cancer, until October 2015. The systematic reviews, which did not include any randomized controlled trials, were excluded from the study. All of the other reviews were included in the study after those two authors assessed the full copies of reviews. A special form was designed in Microsoft Excel 2013 and data extraction was done by the means of that. Data forms had three main parts; the first part was designed for recording the details of the reviews, such as publication year, the authors and number of included RCTs.

The second part was designed to record the risk of bias in domains of selection, performance, detection, attrition, reporting and other biases for each systematic review according to biases in their included RCTs. In addition, the last part was prepared to know whether the authors reached the adequate evidence and a particular conclusion for the study or not.

The data was analyzed by Microsoft Excel 2013 for frequency analyses. In addition, Systematic Reviews were assessed qualitatively, to determine whether the use of Cochrane collaboration's tool for risk of bias had any effect on increasing quality of systematic reviews.

Findings:

The search identified 50 reviews that 3 of them were excluded for not including any RCTs. Finally, 587 RCTs were included for analysis. The detailed information about included systematic reviews and the number of reported biases in different domains for randomized controlled trials are listed in Table 1.

The frequency of RCTs that have reported the risk of bias in each bias domain among all of 587 RCTs are shown in Figure 1.

The frequency of high, low and unknown risk of bias in each bias category among RCTs that have reported considered kind of bias, are shown in Figure 2.

Finally, we found that 33 systematic reviews could finally reach a conclusion due to an adequate amount of evidence. In addition, other 14 reviews required more studies to reach a conclusion.

Discussion:

This study showed that the most and the least reported bias were allocation concealment (selection bias) and detection bias, respectively, which was reported in 93.6% and 48.2% of RCTs.

48% of reports showed the unclear risk of bias for allocation concealment, as the most reported bias in this domain. But, for the other domains, low risk of bias was reported the most, with 42.2%, 51.6%, 45.9%, 54.5%, 62.3% and 53% for adequate sequence generation, performance, detection, attrition, reporting, and other biases, respectively.

According to the results, there was not any systematic review with the only low risk of bias in all categories, so it is concluded that enough high-quality RCTs lack in the field of breast cancer. In other words, almost all of included trials had a high or unclear risk of bias. However,

it should be noted that systematic reviews, which were published in the recent years had a lower risk of bias and were more reliable than the old ones.

The findings of the study confirm the results of a previous study that has been done by Armajio-Olivo in 2014. In this article, 17 Cochrane reviews in physical therapy were studied and it was concluded that most of the included trials in Cochrane studies have a high or unclear risk of bias with the use of Cochrane risk of bias tool. It seems that one reason for lacking high-quality studies in this field is the difficulty of blinding patients and evaluators in all aspects of research. For example, it is impossible to blind patients in the application of some procedures because of their nature. In addition, using a placebo or some procedures may be harmful in some cases, so administration of them should be limited in those cases.

On the other hand, one of the most important reasons for the issue is unreliability of Cochrane Risk of Bias tool. Two studies evaluated the reliability of this tool by comparing results of risk of bias assessments done by Cochrane review authors with external blinded assessors. Results of studies reported poor reliability for Cochrane Risk of Bias Tool (58, 59).

Conclusion:

The results of this study showed that bias is a non-removable part of the research. However, it was considered that RCTs have improved reporting bias due to the application of the new strategies during the last decades, but more improvements for Cochrane risk of bias tool is still necessary. Hence, we recommend that researchers should pay more attention in selecting and blinding of patients and evaluators, choosing the type of interventions, and reporting the results of the study. In addition, we suggest health care

providers, to use the last version of systematic reviews, because of their more reliability.

Conflicts of Interest:

The authors declared that there is no conflict of interest regarding the publication of this paper.

Acknowledgment:

Special thanks to Evidence-Based Medicine Center of Excellence and Student's Research Committee of Tabriz University of Medical Sciences for their support in preparing this study.

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Tables and Charts:**Table 1: Reported risk of bias in RCTs of included systematic reviews**

Title		Selection bias		Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Other Bias
		allocation concealment	Adequate sequence generation					
Addition of drug/s to a chemotherapy regimen for metastatic breast cancer(11)	High	1	1	-	-	-	-	7
	Unclear	16	18	22	22	3	6	5
	Low	5	3			19	16	10
Antitumour antibiotic containing regimens for metastatic breast cancer(12)	High	-	-	-	-	-	-	-
	Unclear	36	-	-	-	-	-	-
	Low	11	-	-	-	-	-	-
Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women(13)	High	-	-	8	8	-	-	-
	Unclear	2	9	1	1	-	-	-
	Low	23	12	15	15	-	-	-
Benzo-pyrones for reducing and controlling lymphoedema of the limbs(14)	High	-	-	-	-	-	-	-
	Unclear	-	-	-	-	-	-	-
	Low	-	-	-	-	-	-	-
Bisphosphonates and other bone agents for breast cancer(15)	High	-	1	14	14	5	2	1
	Unclear	26	24	-	-	4	4	4
	Low	8	9	20	20	25	28	29
Cancer genetic risk assessment for individuals at risk of familial breast cancer(16)	High	1	1	-	-	3	-	-
	Unclear	7	3	-	-	2	1	-
	Low	-	4	-	-	3	7	-
Chemotherapy alone versus endocrine therapy alone for metastatic breast cancer(17)	High	-	-	-	-	-	-	-
	Unclear	8	-	-	-	-	-	-
	Low	2	-	-	-	-	-	-
Chinese medicinal herbs to treat the side-effects of chemotherapy in breast cancer patients(18)	High	-	-	-	-	-	-	-
	Unclear	4	-	-	-	-	5	-
	Low	3	-	-	-	-	2	-
Combination versus sequential single agent chemotherapy for metastatic breast cancer(19)	High	1	-	1	-	-	3	7
	Unclear	9	9	11	10	3	2	
	Low	2	3		2	9	7	5
Conservative interventions for preventing clinically detectable upper-limb lymphoedema in patients who are at risk of developing	High	3	1	1	3	3	1	5
	Unclear	1	1	7	3	1	2	4
	Low	6	8	2	4	6	7	1

lymphoedema after breast cancer therapy(20)								
Exercise for women receiving adjuvant therapy for breast cancer(21)	High	-	-	-	-	-	-	-
	Unclear	5	-	-	-	-	-	-
	Low	6	-	-	-	-	-	-
Exercise interventions for upper-limb dysfunction due to breast cancer treatment(22)	High	1	2	1	3	1	-	-
	Unclear	-	-	-	1	-	-	-
	Low	23	9	4	9	10		
Fibrin glue instillation under skin flaps to prevent seromarelated morbidity following breast and axillary surgery(23)	High	13	10	13	13	17	2	6
	Unclear	-	-	-	-	-	-	-
	Low	5	8	5	5	1	16	12
Follow-up strategies for women treated for early breast cancer(24)	High	-	-	-	-	-	-	-
	Unclear	1	-	-	-	-	-	-
	Low	3	-	-	-	-	-	-
Fraction size in radiation treatment for breast conservation in early breast cancer(25)	High	-	-	-	-	2	-	4
	Unclear	1	1	-	-	1	4	-
	Low	3	3	-	4	1	-	-
High dose chemotherapy and autologous bone marrow or stem cell transplantation versus conventional chemotherapy for women with early poor prognosis breast cancer(26)	High	-	-	-	-	-	-	-
	Unclear	-	-	-	-	-	-	-
	Low	-	-	-	-	-	-	-
High dose chemotherapy and autologous bone marrow or stem cell transplantation versus conventional chemotherapy for women with metastatic breast cancer(27)	High	-	-	-	-	-	-	-
	Unclear	3	-	-	-	-	-	-
	Low	10	-	-	-	-	-	-
Immediate versus delayed reconstruction following surgery for breast cancer(28)	High	-	-	1	1	1	-	-
	Unclear	1	1	-	-	-	-	-
	Low	-	-	-	-	-	1	
Interventions for relieving the pain and discomfort of screening mammography(29)	High	1	1	-	-	-	1	
	Unclear	4	1	4	1	5	-	-
	Low	2	1	3	2	-	-	-
LHRH agonists for adjuvant therapy of early breast cancer in premenopausal women(30)	High	-	-	-	-	-	-	-
	Unclear	8	-	-	-	-	-	-
	Low	6	-	-	-	-	-	-
Manual lymphatic drainage for lymphedema following breast cancer treatment(31)	high	1	1	4	4			
	Unclear	2	1	1	1		1	
	low	3	4	1	1	6	5	
Multidisciplinary rehabilitation for follow-up of	high	2	0	2	2	1	-	-
	Unclear	-	2	-	-	1	1	-

women treated for breast cancer(32)	low	-	-	-	-	1	-	
Non-hormonal interventions for hot flushes in women with a history of breast cancer(33)	high	-	-	2	2	1	4	-
	Unclear	7	4	0	1	11	11	-
	low	9	12	14	13	4	1	-
Partial breast irradiation for early breast cancer(34)	high	1	-	-	1	1	2	-
	Unclear	1	1	1	-	3	2	-
	low	2	3	3	3	-	-	-
Physical therapies for reducing and controlling lymphedema of the limbs(35)	high	-	-	-	3	2	-	-
	Unclear	3	2	-	-	-	-	-
	low	-	1	-	-	1	-	-
Platinum containing regimens for metastatic breast cancer(36)	high	-	-	-	-	-	-	-
	Unclear	9	-	-	-	-	-	-
	low	4	-	-	-	-	-	-
Post-operative radiotherapy for ductal carcinoma in situ of the breast(37)	high	-	-	4	4	-	-	-
	Unclear	-	-	-	-	1	2	-
	low	4	4	-	-	3	2	-
Postoperative tamoxifen for ductal carcinoma in situ(38)	high	1	-	1	1	-	-	-
	Unclear	1	1	1	1	1	-	-
	Low	-	1	-	-	1	2	-
Preoperative chemotherapy for women with operable breast cancer (39)	High	-	-	-	-	-	-	-
	Unclear	8	-	-	-	-	-	-
	Low	6	-	-	-	-	-	-
Prophylactic mastectomy for the prevention of breast cancer(40)	High	23	23	-	15	31	-	-
	Unclear	-	-	-	3	-	-	-
	Low	15	15	38	20	7	-	-
Psychological interventions for women with metastatic breast cancer(41)	High	-	-	-	-	1	-	-
	Unclear	3	4	-	8	2	5	-
	Low	7	6	10	2	7	5	-
Regular self-examination or clinical examination for early detection of breast cancer(42)	High	-	-	-	-	-	-	-
	Unclear	3	-	-	-	-	-	-
	Low	-	-	-	-	-	-	-
Primary prophylactic colony-stimulating factors for the prevention of chemotherapy-induced febrile neutropenia in breast cancer patients (43)	High	1	1	-	1	-	1	2
	Unclear	5	5	-	3	5	4	3
	Low	2	2	8	4	3	3	3
Screening for breast cancer with mammography(44)	High	5	7	-	7	7	6	10
	Unclear	5	3	-	-	-	1	-
	Low	5	5	15	8	8	8	5
	High	-	-	-	1	1	-	-
	Unclear	3	1	1	1	-	2	-

Sequencing of chemotherapy and radiotherapy for early breast cancer (45)	Low		2	2	1	2	1	-
Single agent versus combination chemotherapy for metastatic breast cancer (46)	High	1	3	-	-	4	7	-
	Unclear	33	31	-	-	10	9	-
	Low	14	14	-	-	34	32	-
Specialist breast care nurses for supportive care of women with breast cancer (47)	High	-	-	-	-	-	-	-
	Unclear	3	-	-	-	-	-	-
	Low	2	-	-	-	-	-	-
Strategies for increasing the participation of women in community breast cancer screening (48)	High	-	-	-	-	-	-	-
	Unclear	12	-	-	-	-	-	-
	Low	2	-	-	-	-	-	-
Surgery versus primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus)(49)	high	-	-	-	-	-	-	-
	Unclear	4	4	8	8	-	1	-
	low	3	3	-	-	8	7	-
Systemic therapy for treating locoregional recurrence in women with breast cancer(50)	high	-	-	-	-	-	-	-
	unclear	2	-	-	-	-	-	-
	low	2	-	-	-	-	-	-
Taxane containing regimens for metastatic breast cancer(51)	high	-	-	-	-	-	-	-
	Unclear	7	-	-	-	-	-	-
	low	3	-	-	-	-	-	-
Taxanes for adjuvant treatment of early breast cancer(52)	high	-	-	-	-	-	-	-
	unclear	3	-	-	-	-	-	-
	low	9	-	-	-	-	-	-
Toremifene versus tamoxifen for advanced breast cancer(53)	high	-	-	-	-	-	-	-
	unclear	2	3			3	2	
	low	5	4		7	4	5	
Trastuzumab-containing regimens for metastatic breast cancer(54)	high	-	-	7	-	-	-	-
	Unclear	4	6	-	-	6	-	-
	low	3	1	-	7	1	7	-
Trastuzumab containing regimens for early breast cancer(55)	high	-	-	7	2	2	3	-
	Unclear	6	2	1	-	1	3	-
	low	2	6	-	-	5	2	-
Vascular-endothelial-growth-factor (VEGF) targeting therapies for endocrine refractory or resistant metastatic breast cancer (56)	high	1	1	-	-	-	1	-
	Unclear	2	7	-	-	2	1	-
	low	6	1	-	-	7	7	-
Wound drainage after axillary dissection for carcinoma of the breast (57)	high	2	2	-	4	1	2	2
	Unclear	4	2	7		1	-	1
	low	1	3	-	3	5	5	4

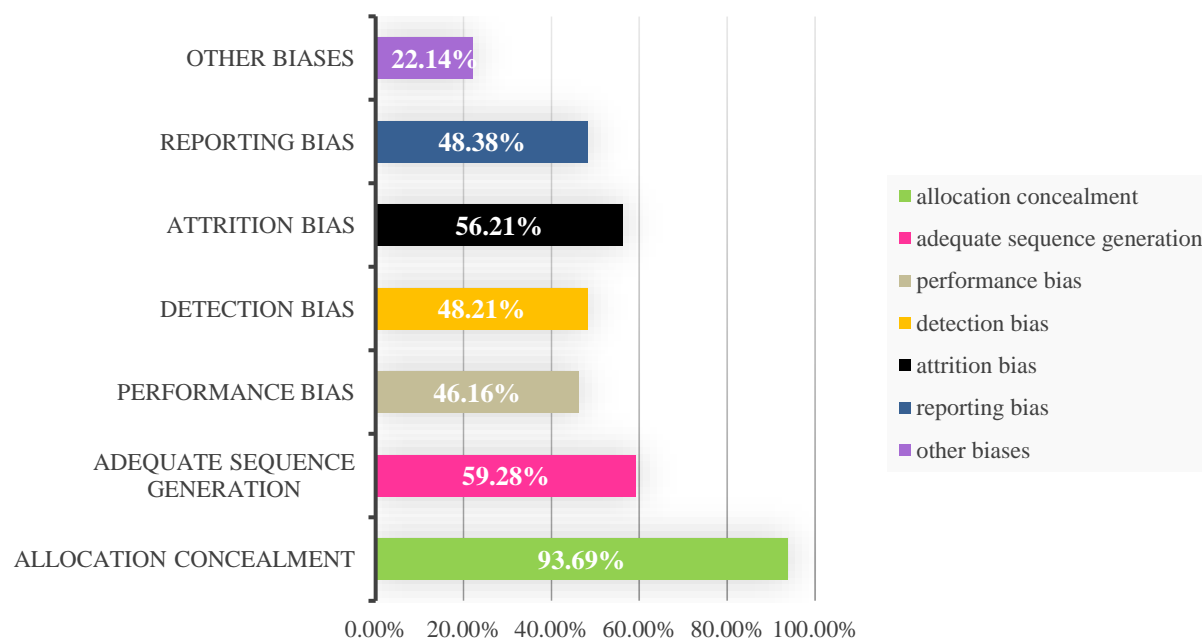


Figure 1. Frequency of reported biases among all RCTs

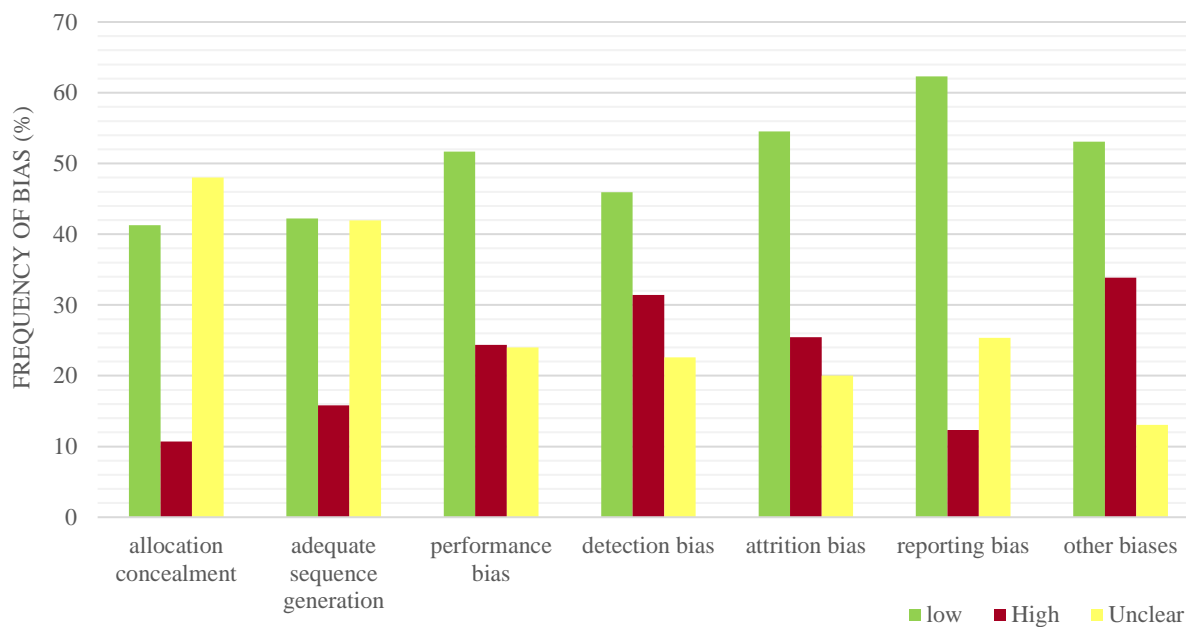


Figure 2. Risk of bias in each bias domain among RCTs that reported considered bias